Universitätsspital Zürich
Klinik für Viszeral- und Transplantationschirurgie
Direktor: Prof. Dr. med. Pierre-Alain Clavien PhD

Arbeit unter Leitung von Dr. med. Dr. sc. nat. Kuno Lehmann

Where Oncologic and Surgical Complication Scoring Systems Collide: Time for a New Consensus for CRS/HIPEC

INAUGURAL-DISSERTATION
zur Erlangung der Doktorwürde der Humanmedizin
der Medizinischen Fakultät
der Universität Zürich

vorgelegt von
Dilmurodjon Eshmuminov

Genehmigt auf Antrag von Prof. Dr. med. P. A. Clavien
Zürich 2016

Publikationshinweis

Titel der Publikation: Where Oncologic and Surgical Complication Scoring Systems Collide: Time for a New Consensus for CRS/HIPEC

Publiziert online am: 15 December 2015

Journal: World Journal of Surgery
http://www.ncbi.nlm.nih.gov/pubmed/26669784

Publication

Acknowledgements

This study and thesis was conducted under guidance of Prof. Clavien, whom I am very grateful.

I would like to express my sincere gratitude to Dr. Lehmann for his excellent support and guidance.

Further I would like to express my thanks Dr. Slankamenac for helping with the statistical analysis and interpretation of results.

Begleittext zur Publikation (equal contribution)

Von Dilmurodjon Eshmuminov

Background

Peritoneal carcinomatosis is considered as a terminal stage of many gastrointestinal tumors.[1-3] Systemic Chemotherapy improves outcomes but does very rarely offer long-term survival.[1, 4] In the last three decades, cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has provided promising results regarding patient survival.[1, 2] Currently, CRS combined with HIPEC is considered as a standard treatment for malignant peritoneal mesothelioma[3, 5] and pseudomyxoma.[3, 6] Good results and significant survival benefits after CRS and HIPEC were also shown for selected patients with peritoneal metastasis from colorectal cancer.[7] However the survival benefit is achieved at the cost of increased morbidity and mortality due to an extensive surgery and intraoperative chemotherapy. The reported major complication rates after CRS and HIPEC range from 25% up to 60%, which is an important argument for many physicians against CRS/HIPEC.[8, 9] To standardize the reporting of complications after CRS and HIPEC, the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) was proposed during the consensus conference in Milan in 2006.[9] This recommendation is not uniformly accepted. In contrast, the therapy-oriented Clavien-Dindo classification of surgical complications is widely used and validated in other fields of surgery.[10-12] Yet, the use of two different classification systems in the reporting of postoperative outcomes creates dilemma in interpretation and comparison postoperative outcomes in the field of CRS/HIPEC.

We therefore designed this study to analyze postoperative complications after CRS/HIPEC. In a first step we reviewed the postoperative complications in our patients cohort after CRS/HIPEC. In a further step, we compared the two classification systems CTCEA and Clavien-Dindo with regards to reproducibility, simplicity and accuracy.

Patients and methods

Patients

Complications were recorded in 147 consecutive patients, admitted with primary or secondary peritoneal malignancy. The complication grade determined according to the CTCAE and the Clavien-Dindo classification. Clavien-Dindo grades IIIb-IV and CTCAE grades III-IV were considered as ‘‘major’’ complication. The local ethical review board approved the study protocol (KEK-ZH-Nr. 2015-0269).

Survey questionnaire and raters

A questionnaire with randomly selected complications was designed. The severity grade of selected cases was defined after discussion by expert board. The raters were asked to define their level of certainty and the simplicity of the scores in a visual analog scale ranging from 0 to 10. A separate field was provided to define the grade of complication and the duration of time spent to decide upon the complication grade. Fluency in English was prerequisite, thus the classifications were provided only in English.

Fifty-four residents, 30 experienced attending surgeons and 28 medical oncologists were contacted to answer the questionnaire with a set of complications. The raters were randomized to evaluate the similar questionnaire with either the CTCAE or the Clavien-Dindo classification and received uniform introduction in the same way throughout the survey. Some surgeons had experience with the Clavien-Dindo classification and all medical oncologists had experienced with the CTCEA, since unfamiliarity with some of the grading systems was not mandatory for raters. No reimbursement was provided for participation. The questionnaire was submitted anonymously. Up to three reminders were sent to raters per e-mail or phone, if there was no response. Four study nurses trained in the Clavien-Dindo classification were contacted to evaluate the same questionnaire. Study nurses trained in CTCEA were not available for the survey.

Results

Morbidity and mortality after CRS/HIPEC

The study cohort includes 83 female and 64 male patients with a median age of 53 years. Peritoneal carcinomatosis of appendicular origin was the commonest, followed by colorectal cancer, mesothelioma, ovarian cancer and gastric cancer. Overall, 37 % (54/147) patients had at least one postoperative complication. The major complication rate was 8.1% according to the Clavien-Dindo classification (grades IIIb-IV). Grading of the same complications according to the CTCAE (grades III-IV) showed this rate at 25.1% of the patients and was significantly higher compared to Clavien-Dindo classification (8.1 vs. 25.1 %, p = 0.0001). Assessment of multiple complications per patient revealed totally 86 complications as a unit in 54 patients. Analysis of these 86 complications as a unit showed that intestinal complications, e.g., anastomotic insufficiency, fistulas or abscess 19.8% (17/86), pulmonary complications 19.8% (17/86) and ileus 15.1 (13/86) were most frequent one. 76% (65/86) of complications were graded as “minor” (less than grade IIIb according to Clavien-Dindo classification) and respectively could be managed without redo-surgery or admission to intensive care unit. The mortality rate was 2% (3/147). In one case the patient died due to postoperative bleeding secondary to a pancreas fistula, one patient developed fatal pulmonary failure in postoperative course and in third case a duodenal fistula with sepsis and a complicated course lead to death.

Results of survey

The response rate was among residents 74% (40/54), among seniors 70% (21/30) and among oncologists 75 % (21/28). All three groups assessed more correctly with Clavien-Dindo classification compared to the CTCAE classification: residents (62 vs. 32 %, p<0.001), surgeons (66 vs. 28 %, p<0.001) and oncologists (74 vs. 31 %, p<0.001). Of note higher rate of correct answers required less time to complete the questionnaire with Clavien-Dindo classification compared to CTCEA classification for residents (8 ± 4 min vs. 22 ± 10 min, p<0.001) as well as for surgeons (9 ± 5 vs. 19 ± 7, p = 0.006). The difference in time requirements for oncologists

was statistically not significant (16 ± 11 vs. 23 ± 15, p = 0.4). Remarkably Clavien-Dindo classification showed also good inter-rater reliability among residents (0.67, p<0.001), surgeons (0.72, p<0.001) and oncologists (0.82, p<0.001), which was only moderate for CTCEA for all groups (residents: 0.34, p<0.001, surgeons: 0.45, p<0.001, oncologists: 0.39, p<0.001). Consistently, all three groups considered the Clavien-Dindo classification as more simple compared to the CTCAE classification: residents 7.1±2.2 vs. 4.5±2.3, p<0.001, surgeons 8.4±0.8 vs. 4.1±2.9, p = 0.001 and oncologists 8 ± 1.5 vs. 5 ± 2.1, p = 0.03. Subjective assessment of certainty was higher with Clavien-Dindo classification compared to CTCEA classification only for surgeons (8.4 ± 0.9 vs. 5 ± 2.7, p = 0.005). Residents (6.2 ± 1.9 vs. 5.4 ± 1.5, p = 0.2) and oncologists (7.5 ± 1.2 vs. 6 ± 1.8, p = 0.1) showed similar certainty with both classifications.

Four personnel trained in the Clavien-Dindo classification showed the highest rate of correct answers at 98 % (47/48).

Conclusion

In conclusion, we observed different interpretation of severity grades of postoperative complications after CRS/HIPEC between Clavien-Dindo and CTCEA classifications. Consistent reporting system of postoperative complications is urgently needed in the field of CRS/HIPEC. The optimal classification system for reporting complications after CRS/HIPEC should be defined by new consensus.

My own contribution in current scientific work

Manuscript:

- I drafted the first version of the manuscript, tables and figures and edited it after critical comments by Dr. Lehmann. Dr. Lehmann made the final changes prior to submission to the journal.
- With the help of Dr. Lehmann I revised the manuscript and made changes after comments of journal reviewers, including new data.

Patients:

- I retrieved from clinical charts patient's data for time period 2012-2013.
- I drafted the study protocol for local ethical review board and submitted the final version after approval and signature by Dr. Lehmann.
- I performed a statistical analysis under supervision of Dr. Lehmann.

Survey questionnaire and raters:

- The expert board defined the grade of selected complications.
- I drafted the questionnaire with the predefined complications set and edited after critical comments by Dr. Lehmann.
- I recruited, randomized and send reminders to the raters.
- I retrieved the data from the questionnaire for analysis.
- I did statistical analysis of the data from questionnaire with the help of Dr. Lehmann and Dr. Slankamenac.

References

1. Glehen O, Mohamed F, Gilly FN Peritoneal carcinomatosis from digestive tract cancer: new management by cytoreductive surgery and intraperitoneal chemohyperthermia The lancet oncology 2004: 5; 219-228

2. Roviello F, Caruso S, Marrelli D*, et al.* Treatment of peritoneal carcinomatosis with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: state of the art and future developments Surgical oncology 2011: 20; e38-54

3. Sommariva A, Pilati P, Rossi CR Cyto-reductive Surgery combined with Hyperthermic Intra-peritoneal Chemotherapy for Peritoneal Surface Malignancies: current treatment and results Cancer treatment reviews 2012: 38; 258-268

4. Franko J, Shi Q, Goldman CD*, et al.* Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841 Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012: 30; 263-267

5. Yan TD, Welch L, Black D*, et al.* A systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignancy peritoneal mesothelioma Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2007: 18; 827-834

6. Sugarbaker PH New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome? The lancet oncology 2006: 7; 69-76

7. Elias D, Gilly F, Boutitie F*, et al.* Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010: 28; 63-68

8. Pelz JO, Germer CT [Morbidity and mortality of hyperthermic intraperitoneal chemoperfusion] Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen 2013: 84; 957-961

9. Younan R, Kusamura S, Baratti D*, et al.* Morbidity, toxicity, and mortality classification systems in the local regional treatment of peritoneal surface malignancy Journal of surgical oncology 2008: 98; 253-257

10. Clavien PA, Strasberg SM Severity grading of surgical complications Annals of surgery 2009: 250; 197-198

11. Dindo D, Demartines N, Clavien PA Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey Annals of surgery 2004: 240; 205-213

12. Slankamenac K, Graf R, Barkun J*, et al.* The comprehensive complication index: a novel continuous scale to measure surgical morbidity Annals of surgery 2013: 258; 1-7

Curriculum Vitae

Dilmurodjon Eshmuminov

09.03.1983	Born in Andijan, Uzbekistan
1990-1999	Secondary education (high school) in Yakkobag, Uzbekistan
1999	Certificate of completion of secondary (high school) education
1999-2006	Medical education at Tashkent Medical Academy, Uzbekistan
2006	The Uzbek Medical State Examination, Tashkent Medical Academy, Uzbekistan; General Practitioner (MD)
2006-2009	Master study in Surgery, Tashkent Medical Academy, Uzbekistan; Master`s Diploma in Surgery
2009-2011	Visiting doctor and research assistant, Department of Visceral and Transplantation Surgery, University Hospital Zurich
2010	The Swiss Medical State Examination, University of Bern, Switzerland
2011-2012	Residency in Surgery, Spital Herisau
2012 – currently	Residency in Surgery Department of Visceral and Transplantation Surgery, University Hospital Zurich